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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/965,528	09/26/2001	Y. Tom Tang	PF-0701 USA	3765

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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	8

DATE MAILED: 08/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/965,528	TANG ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this c mmunication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12-3-01 and 19 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11,12,30-45 and 71* is/are pending in the application.

4a) Of the above claim(s) *1,12,30,33,35,44,45 and 71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11, 31-32,34, 36-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1, 11, 12, 30-45 and 71 are pending.

2. Applicant's election with traverse of Group LIV, claims 11, 31-32, 34 and 36-43, filed on 6-19-02, is acknowledged.

Applicant's traveral is on the grounds that the restriction is unduly multiplied, and search for antibodies that bind specifically to a polypeptide of SEQ ID NO:16 will necessarily encompass a search for the polypeptide itself, variants and fragments thereof, and polynucleotides encoding the polypeptide. Further the extending the search and examination to the pending claims would be far less of a burden for the examiner. This is not found persuasive because the Groups XVI, XLII, LIV and CXIX-CXXII are classified in different Classes and are recognized divergent subject matter. Specifically, Group XVI (now claims 1 and 71) recites polypeptide of SEQ ID NO: 16, Group XLII (now claim 12) recites polynucleotide of SEQ ID NO:42, Group LIV recites an antibody while Groups CXIX and CXX recite in vivo and in vitro diagnosing methods using the antibody of Group LIV. Group CXXI recites methods of detecting using the antibody of Group LIV while Group CXXII recites a method of purifying. The methods and compounds recited, therefore, in the restriction between Groups XVI, XLII, LIV and CXIX-CXXII are proper. Therefore the methods and compounds recited are distinct and independent, and searches of all groups would place an undue burden upon the examiner due to the distinct and separate classification of each Group.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1, 12, 30, 33, 35, 44, 45 and 71 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 11, 31, 32, 34, and 36-43 are under examination.

5. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in the United States on May 19, 2000. It is noted, however, that applicant has not filed a certified copy of the PCT/US00/13975 application as required by 35 U.S.C. 119(b).
6. The specification on page 1 should be amended to reflect the relationship of PCT application No. PCT/US 00/13975 with the instant application.

7. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The specification on page 56, line 29, contains hyperlinks. The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference.

8. The amendment filed 12-03-01 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The preliminary amendment filed on 6-19-02 to the paragraph beginning at page 26, lines 23 and ending on page 27, line 2 substituting SEQ ID NO: 43 with SEQ ID NO: 42 represents a departure from the specification and the claims as originally filed. Applicant points out to USSN 60/144,270, filed July 15, 1999 for support. However, the specification and the claims as originally filed have no support for the new replacement of SEQ ID NO: 43 with SEQ ID NO: 42. It is noted that Table 3 shows SEQ ID NO: 42 to be expressed in Gastrointestinal tissue but not islet cells and islet cell tumor.

Applicant is required to cancel the new matter in the response to this Office action.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 34 are 36-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 34 has no antecedent basis in base claim 32, because claim 32 recites a composition comprising an antibody per se, whereas a labeled antibody is recited in claim 34.

B. The term "specificity" recited in claim 36, line 1 and claim 39, line 1 is ambiguous and unclear and the metes and bounds of the claimed "specificity" is not defined.

5. 35 U.S.C. § 101 reads as follows:
"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

6. Claims 11, 31, 32, 34 and 36-43 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility.

Applicants are directed to the Revised Interim Utility Guidelines, Federal Register, Vol. 64, No.244, pages 71427-71440, Tuesday December 21, 1999. In keeping with the revised utility guidelines and corresponding training materials (available on the PTO Website), none of the disclosed uses is a specific and/or substantial use.

7. The instant application has provided a description of an isolated polypeptide and an antibody against the polypeptide. The instant application does not disclose the biological role of the polypeptide or its significance. The instant specification asserts specific utilities for the claimed invention that specifically expressed in islet cells and in islet cell tumor only (on pages 26, lines 33-34 in particular). The specification also asserts that the claimed extracellular signaling molecules (EXCS) is acknowledged by the Applicants to have diverse biological effects (see page 36, lines 8-13) and proteins containing signature sequences and motifs similar to extracellular signaling molecules (EXCS) are disclosed to be involved with reproductive, cardiovascular, nervous, gastrointestinal, cancerous, hematopoietic/immune, cell proliferative and inflamed tissue (see page 36, lines 5-10). The specification also asserts that the claimed antibody could be for therapeutic use, page 39, line 21, in a pharmaceutical composition, page 43, lines 20-23) to treat or prevent a disorder associated with decrease expression or activity of EXCS such as disorders disclose on pages 36-38. Further, the specification asserts that antibodies which specifically binds EXCS may be used for the diagnosis of disorder characterized by expression of EXCS, or in assays to monitor patients being treated with EXCS or agonists, antagonists, or inhibitors of EXCS (see page 46, lines 14-16), among others.

These utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for EXCS. The disclosed polypeptide is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After further research, specific and substantial credible utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. Applicant directed the Examiner's attention to page 26 lines 23-35 for the uses of SEQ ID NO:42 which is " expressed specifically in islet cells and in islet cell tumor only". First, Leiter et al (J Biol Chem 260:13013-13017, 1985) indicate that using Southern blot analysis of SEQ ID NO: 42 homolog, the gene detected in a pancreatic polypeptide-producing islet cell tumor was indistinguishable from that in normal human leukocytes (see abstract and page 13016, right column 2nd paragraph in particular), therefore, "expressed specifically" dose not exclude other non-islet cells from expressing SEQ ID NO: 42. Second, since the SEQ ID NO: 42 is "specifically expressed" in both normal and tumor islet cells then, methods of identifying or

therapeutic regiments would act on both normal and tumor cells. Third, no single effect of the disclosed SEQ ID NO: 42 is ascribed to the protein, as well as to the claimed antibody which specifically binds to the protein. The presence of a polynucleotide of SEQ ID NO: 42 in Islet cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the polypeptide, which is encoded by the polynucleotide, and the disease.

The instant situation is directly analogous to that which was addressed in *Brenner V. Manson*, 148 U.S. P. Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S. C. § 101, which requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The instant claims are drawn to a polypeptide of as yet undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that the EXCS of the instant application was, as of the filling date, involved with reproductive, cardiovascular, nervous, gastrointestinal, cancerous, hematopoietic/immune, cell proliferative and inflamed tissue as stated at page 36, lines 5-10 of the specification. Until some actual and specific significance can be attributed to the protein identified in the specification as EXCS, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Thus, there was no immediately apparent or "real world" utility as of the filing date.

No single effect of the disclosed EXCS is ascribed to the claimed protein and hence to the antibodies against those proteins. Note that while the specification produces the full-length protein recombinantly, no biological activity is established for the full length protein or any of the claimed fragments thereof. As such, further research would be required to identify or research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved would be required. Since the instant specification does not disclose a credible "real world" use for EXCS, then the claimed invention as disclosed does not meet the requirements of 35 U.S. C. § 101 as being useful.

The proteins of the instant invention are compounds, which share some structural similarity with extracellular singling molecule proteins based on sequence similarity. It is not clear if the protein of the instant application would have the same function in reproductive, cardiovascular, nervous, gastrointestinal, cancerous, hematopoietic/immune, cell proliferative and inflamed tissue as stated at page 36, lines 5-10 of the specification. Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000; 18(1):34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the

multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Finally, even single amino acid differences can result in drastically altered functions between two proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). To employ a protein of the instant invention in any of the disclosed methods would clearly be using it as the object of further research. Such a use has been determined by the courts to be a utility which, alone, does not support patentablility. Since the instant specification does not disclose a credible "real world" use for EXCS, then the claimed invention as disclosed does not meet the requirement of 35 U.S.C. § 101 as being useful.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 11, 31, 32, 34, and 36-43 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to used the claimed invention.

10. Claims 11, 31, 32, 34 and 36-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

Further, besides an isolated antibody which binds to a polypeptide of SEQ ID NO: 16, the specification fails to provide any guidance as to how to make any antibody which specifically binds to any polypeptide **comprising** a naturally occurring amino acid sequence **at least 90%** identical to the amino acid sequence of SEQ ID NON:16 in claim 11(b); any antibody which specifically binds to any **biologically active fragment** of a polypeptide or any **immunogenic fragment** of a polypeptide having the amino acid sequence of SEQ ID NO: 16 in claim 11(c-d), any composition comprising any antibody in claim 32, or a method of preparing/making a polyclonal/monoclonal antibody with the **specificity** of the antibody of the embodiment of claim 11 in claims 36 and 39. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There is insufficient guidance and direction as to how to make the claimed antibodies, wherein the antibodies which specifically binds to any polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO: 16; any biologically active fragment or any antibody to a immunogenic fragment of a polypeptide of SEQ ID NO:16.

The present specification fails to provide sufficient disclosure of biologically active or immunogenic fragments of SEQ ID NO: 16, or a polypeptide at least 90% sequence identity to the sequence of SEQ ID NO:16 which include numerous changes and variation. The specification does not provide sufficient guidance as to which of the amino acids may be changed while the biological activity is retained. In addition, the term "comprising" in claim 11b is open-ended, it expand the "naturally occurring polypeptide" to include additional non disclosed amino acids. Further, the specification fails to provide guidance on how to measure and determine the antibody "specificity", and further to make or prepare an antibody that would have that same "specificity".

Colman *et al* in Research in Immunology (145(1):33-36, 1994) teach single amino acid changes in an antigen can effectively abolish antibody antigen binding. Abaza *et al* in Journal of Protein Chemistry (11(5):433-444, 1992) teach that single amino acid substitutions outside the antigenic site on a protein effect antibody binding. Further, Lederman *et al* in Molecular Immunology (28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Additionally, Li *et al* in PNAS (77:3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document).

Because of the unpredictability and the lack of guidance, an undue experimentation would be required to determine which modifications would be acceptable to retain occluding structural and functional activity, and the fact that the relationship between the sequence of a protein/peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Ngo *et al* in the Protein Folding problem and Tertiary Structure prediction, 1994, Merz *et al.*, (ed), Birkhauser, Boston, MA, pp.433 and 492-495), it would require an undue amount of experimentation for one of skill in the art to arrive at *biologically active and immunogenic fragments* or *a naturally occurring amino acid sequence at 90% identical to an amino acid sequence of SEQ ID NO:16* encompassed by the claimed invention.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

11. Claims 11, 31, 32, 34 and 36-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an antibody which specifically binds to a polypeptide of SEQ ID NO:16; however, applicant is not in possession of any antibody which specifically binds to any polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NON:16 in claim 11(b); any antibody which specifically binds to any biologically active fragment of a polypeptide or any immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO: 16 in claim 11(c-d), any composition comprising any antibody in claim 32, or a method of preparing/making a polyclonal/monoclonal antibody with the specificity of the antibody of the embodiment of claim 11 in claims 36 and 39. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
August 12, 2002

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